DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/7/09 has been entered.

Claims 1, 25, 67, and 81 are amended.

Claim 84 is newly presented.

Claims 1-7, 12-32, 37-46, and 67-84 are presently pending.

Election/Restrictions

Applicant has previously cancelled all claims drawn to non-elected inventions.

Claims 1-7, 12-32, 37-46, and 67-84 are presently considered.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/414,097, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The 60/414,097 Application fails to provide any of the data or information available in present Example 4 for support. Such support is the only support provided for the stability of these formulations. Hence, Applicant is denied priority to such document.

Response to Argument – Priority

Applicant argues that while the non-provisional Application to which the Examiner has subjected Applicant's claims to denied priority does not disclose Example 4, nor the specific time frames of stability, does provide support for the composition, and states that the specification also recognized promoting shelf-life of the particles, and hence, possession is had, as the properties are inherent in the composition (pp. 9-10, paragraph bridging).

Such is not persuasive. First, with regard to the support on pp. 3-4, paragraph bridging, of the non-provisional, it is clear that such paragraph discloses the increased stability as being commensurate with the attachment to the inert metal carrier particles, not the specific sub-group of polyArg[x], wherein x is from 2-10. With regard to the citation of p. 18, lines 7-17, the paragraph states that homopolymers of Arg or Lys are preferred, that the homopolymer may range through several mw ranges, and that X may be several ranges, but not from 2-10. With

regard to the second paragraph quoted in these lines, it is clear that X being from 2-10 is limited to "a small peptide", which the specification fails to define, but the presently-examined specification defines "polypeptide" as being a compound or two ro more subunit amino acids, analogs, or mimetics (p. 8, paragraph 3), and hence, the argument has actually mutated due to the new defintion provided. Did Applicant intend this to be applied to Arginine as the invention? In addition, the paragraph of hte non-provisional of p. 18, lines 7-17, provides for Arg(4) and Arg(6), but such does not provide for possession of the larger genera.

Still further, it is noted that Applicant is claiming their "stability" as a "surprising or unexpected property" with regard to the art rejections, below, as well as an "inherent property" of the claims as presently-claimed. It would appear to that this surprising or unexpected property therefore, was not recognized until after the date of priority, and hence, it is not posessed at the time of priority.

Claim Rejections - 35 USC § 112 – Clarity

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claim 81 for self-dependency is withdrawn, as the Claim has been amended to remove such self-dependency.

Claims 1-7, 12-32, 37-46, and 67-83 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as modified by the presently-amendment limitations to half-life.

Claims 1, 25, and 67 each contain the newly-amended generic limitation "wherein the particles suitable for delivery have a half-life of at least 27 days at 40[degrees]C." Such is so broad as to be undefined. The conditions which define the system depend on the fluid the particles are within, the pressure of the system, the exposure to enzymes, acids, bases, and other chemical and biochemical components, as well the length of the DNA, and other components not mentioned (e.g., trehalose? sucrose? salts?) present in the system. For example, the particles, at high or low pH would dissolve the particles, and/or cause digestion of the nucleic acids and proteins and Applicant's own specification teaches the sugars for increasing stability of the particles (e.g., Examples). Hence, the Artisan would not know when the claim was being infringed from such generic limitation as the system is essentially only partly defined.

Claims 1, 25, and 67 are not clear for their metes and bounds. The present amendment appears to indicate that either a composition is claimed in which particles have a specific half-life, or, under an alternative interpretation, appears to claim only those particles which are suitable for delivery and are at least half-active after 20 days at 40 deg. C. Hence, these alternative, non-coextensive interpretations, lead to a lack of clarity such that the Artisan would not understand when he or she is infringing the claim.

Claim 1 is not clear for its metes and bounds. To wit, the particles are described as "obtainable" by depositing the nucleic acid on an inert metal carrier, in the presence of a homopolymer of Arginine and a metal chelating agent, but fails to provide the structure of the particles obtained. When read in the context of Claim 67, which must necessarily have a distinct scope, appears to require the particle to be something other than the scope of Claim 67, and

simply to encompass anything which is a "particle" which is in mixture of the method of making. Hence, the claim fails to provide sufficient structure for the compositions claimed.

Claims 1-7, 12-32, 37-46, and 67-84 are rejected for depending from a rejected base claim and not overcoming the lack of clarity.

Response to Argument – Lack of Clarity

Applicant's argument of 8/7/09 has been fully considered but is not found persuasive.

Applicant argues that because the claims have been amended to recite "at least 27 days", the Artisan would now understand the metes and bounds of the claims, and hence, the claims are adequately provided by the Examples 1 and 2 (p. 10, paragraph 2).

Such is not persuasive. How changing the limitation of "20 days or more" to "at least 27 days" adequately defines the system conditions is completely missed by the Examiner. Further, how enablement issues provide for clarity are simply beyond the Examiner's understanding. Simply put, these claims do not limit the solvent the particles are stored for 27 or more days in, the pH of the system, the pressure, whether other reactants are present, and hence, the system is inadequately defined to determine what is meant.

Applicant argues that MPEP 2173.05(b) provides that, in this case, the term to half-life is well known, and hence, the claim is not indefinite (p. 11, paragraph 1).

Such is not persuasive. First, the term half-life is not disputed here. We all know what it is. What is disputed by the Examiner is whether the conditions for half-life are defined well-enough to define the invention. To wit, Applicant's system defining where the half-life is obtained is simply a temperature. However, it is well-known that acids and basis can digest the metal carriers, and the Examiner's own experience is utilized to back this up. In the mid-1980s,

the Examiner worked in an analytical laboratory, and digested metals with acids and bases to acertain the amounts of trace metals in solutions. Further, it is well known that peptide bonds are subject to acid and base hydrolysis. Further it is well known that the type of solvent or absence thereof will affect the rate of degradation. For example, dried and nitrogen-stored compositions are more stable than those in water with an acid. Hence, it clear that the absence of conditions beyond temperature is so broad as to be indefinite. MPEP 2173.5(b) provides that "When relative terms are used in claims wherein the improvement over the prior art restsentirely upon size or weight of an element in a combination of elements, the adequacy of the disclosure of a standard is of greater criticality", further emphasizing that the system conditions are critically important here, in order to overcome the 103 rejections provided, as Applicant argues that this is an "unexpected" or "surprising" result, as in the arguments under the art rejections below. Hence, it is even more critical to define the conditions here.

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12-32, 37-46, and 67-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for comprising new matter, for reasons of record, as modified by the amendments. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 25, and 67 each contain the newly-amended generic limitation "wherein the particles suitable for delivery have a half-life of greater than 20 days at 40[degrees]C." The balance of the claims depend from these claims, and hence, also require such limitation.

Applicant cites paragraph 10 of the U.S. Patent Publication 2006/0153804 to shown that they contemplated optimizing stability of nucleic acids attached to the particles, and condensing agents in paragraph 65 and homopolymers of Arginine in paragraphs 71-72 (Argument of 8/7/09, p. 12, paragraph 2). And it is further argued that the limitation that the particles are stable with a half-life of at least 27 is simply an inherent property (p. 12, paragraph 2). However, such is not correct. First, Applicant is claiming this limitation as an unexpected or surprising property, to overcome the Art, and hence, by claiming it an inherent property, means that it requires no support. However, by providing such limitation later means that they did not recognize that the property was one of at least 27 days at 40 deg C, at the time of filing. Moreover, such is clearly not an inherent property as one composition measured at 40 deg C only provided 16 days half-life (e.g., TABLE 2). Still further, Arg(4) fails to provide support for the broader genera, as a single embodiment does not provide adequate description for a genera.

Example 4, which is specifically titled "Example 4: Development of tetraarginine formulations", and Tables 2 and 5 for support for the limitation (Id.). Moreover, these particle preparations were derived from subsets of experiments to optimize conditions. Specifically, Example 1 determines specific experiments that demonstrate that specific sugars and salts have differing influences on DNA yield, physical stability of DNA on particles (pp. 25-29), that

precipitations using various ratios of protamine sulfate, EDTA, water, and either trehalose, sucrose, or lactose, provide for similar stability (pp. 29-31), although the actual data of stability is withheld, so the Examiner simply must take the word of Applicant that the stability is similar. However, the cited Example 4 recites in TABLE 2 a series of individual particles, which are limited to gold, and precipitated with tetraarginine, in the presence of not only EDTA or DTPA, but also sucrose or trehalose. Moreover, the results in TABLE 2 only demonstrate that the control (spermine-condensed) generally provides a lower half-life at either temperature 35 or 40 deg C, however, at 40 deg C, DNA/trehalose/DTPA combination does worse than spermine, and this is the temperature that is claimed. Still further, the conditions of testing are not the conditions implied by the claims, which appears to imply in vivo. Simply put, there is nothing here to convince the Artisan that Applicant considered this to be the genera of particles which Applicant conveyed as their invention at the time of filing, much less the time of priority.

TABLE 5 is a hodge-podge of stabilities of various formulae at various temperatures, and hence, nothing can be gleaned here to determine that Applicant possessed this genera as the invention at the time of filing, much less the time of priority.

Still further, Applicant's own arguments appear to provide a post-filing mix-and-match analysis to provide disclosure to distinguish over the Art, which includes more than simply the temperature and half-life, but specific conditions of use of sugars, chelators, and length of protein which appears to argue for support. Such is simply an obviousness-type support meant to overcome art-supplied rejections, and obviousness simply does not provide for possession of the invention at the time of filing.

Lastly, the Examiner has reviewed the Application as filed and fails to find evidence that Applicant conveyed to the Artisan, either implicit or explicit, that the invention was limited the broad generic particles claimed, with the required properties.

Hence, these claims are properly rejected for comprising new matter.

Response to Argument - New Matter

Applicant's argument of 8/7/09 has been fully considered but is not found persuasive.

Applicant argues several portions for the specification to demonstrate possession at the time of filing (p. 12, paragraph 2).

Such is not persuasive for the reasons given above, in the rejection body. To wit, simply put, there are compositions that Applicant has demonstrated have less stability under the conditions, e.g., TABLE 2, and fall within the claims; there is no explicit recitation to those embodiments which meet the claimed limitation of stability; and the amended limitations are being utilized to overcome a rejection of obviousness under the argument of "surprising" or "unexpected" results, and yet, their own understanding of such results were not realized until an amendment was made during prosecution, and are not explicitly recited, and are not commensurate with the disclosure. Hence, the claims remain rejected for comprising new matter.

Applicant argues that the Examples are not a hodge-podge of data, but provide "numerous formulations" and demonstrate studies to determine stabilities under many distinct conditions and they robustly show greater half-life than with spermidine/CaCl2 precipitation onto the metal particles (p. 12, last paragraph).

Such is not persuasive. At least some of the compositions specifically encompass compositions with lower stabilities as found in the examples, yet lie within the claims, and Applicant's own terminology relies upon later-recognized important properties of stability which were incorporated to overcome an art rejection, yet provides no explicit recitation of a stability required, and is supported by, at best, obviousness, which does not supplant the need to provide possession.

Applicant argues that the single inoperative embodiment of Table 2 does not render the claims unpatentable for enablement (p. 13, paragraph 1).

Such is not persuasive. This has nothing to do with enablement.

Hence, the rejections remain and are applied to the new claim.

Claim Rejections - 35 USC § 103 – Sanford/Balhorn (Oard)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 12-13, 17-20, 22-30, 32, 37, 38, 42-45, 67, and 73 remain rejected, and Claim 84 is newly rejected, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, for reasons of record and as necessitated by amendment.

The reasoning is repeated for clarity of record, and the new claims are addressed:

With regard to Claims 1-3, 7, 13, 17-18, 25, 27, 28, 32, 38, 42-43, and 84 Sanford teaches M-10 series tungsten microprojectile particles (which range from 0.3 to 2.1 micrometers in diameter (e.g., Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, p. 249, col. 1, paragraph 3), coated with DNA condensed in the presence of spermidine, and also in the presence of EDTA (e.g., col. 15, paragraph 2) and also in the presence of calcium chloride (e.g., Id.), and the methods of making claimed (e.g., Id.).

With regard to Claims 4-5, 28-29, Sanford teaches that a transgene for, *inter alia*, kanamycin resistance, is transformed into the cells, and further expressed (EXAMPLE 2). Kanamycin is a fungal protein, and hence, a Fungal antigen.

With regard to Claims 19-20, 44-45, the particles are subsequently contacted with ethanol (e.g., col. 15, paragraph 3).

With regard to Claims 22-24, Sanford teaches a needless syringe device, as it has no needle, but injects the particles into cells (e.g., Figure 1), and which contains a receptacle containing the particles for delivery (e.g., FIGURES 5a-5b).

With regard to Claim 26, Sanford teaches the addition of the spermidine to the mixture containing the microparticles and DNA (e.g., col. 15, paragraph 2).

However, with regard to all rejected claims, Sanford fails to teach the use of arginine of the formula $[Arg]_{2\text{-}10}$ or a physiologically acceptable salt thereof .

However, the purpose of spermidine in condensing the DNA is to provide compact particles, resistant to degradation, as taught in the Art by Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, e.g., p. 230, paragraph bridging columns. Further,

Balhorn teaches that transformations of somatic cells and sperm are improved by the faster release of the DNA from condensation by the use of small polymers of polyArginine, and specifically, for the highest change in off-rate, those between 6-12 arginines having the greatest release kinetics (e.g., p. 233, paragraph bridging columns). Still further, Balhorn teaches that by simply changing the amount of arginines in the polyArginine in such delivery methods, the length of time required to dissociate from the polyArginine could be tailored for each individual delivery system (e.g., p. 233, column 2, paragraph 2), and hence, tetraarginine (Claim 73) would be found upon routine experimentation.

Further, with regard to the presence of EDTA on the surface of the particle (e.g., Claim 67), absent reason to believe otherwise, these particles do have EDTA on their surface.

Hence, at the time of invention, it would have been obvious to modify the microprojectile particles of Sanford with the use of the polyarginines of Balhorn, to arrive at the claimed invention. The Artisan would have been motivated to do so to arrive at the desired release kinetics for any specific system. Moreover, the Artisan would have had a reasonable expectation of success, as Balhorn had already demonstrated the release kinetics to be improved.

Response to Argument – Sanford/Balhorn evidenced by Oard

Applicant's argument of 8/7/09 has been fully considered but is not found persuasive.

Applicant argues that the claimed invention is drawn to particles obtainable by depositing a nucleic acid on inert metal carrier particles in the presence of the polyArg or a physiological salt thereof, and a metal ion chelating agent, and thus requires both during deposition in order to have the "synergistic" effect on stability of the claimed particles (p. 14, paragraph 2).

Such is not persuasive. There is nothing in the claim that is not demonstrated as obvious. The "synergistic" effect on stability is not nothing more than what Applicant has determined to be "optimization" of conditions, and not a suprising or unexpected property (e.g., specification, p. 3, penultimate paragraph). Further, Sanford does teach the presence of EDTA in the precipitating solution, and as shown, it was obvious to substitute the Arginine peptide of Balhorn. Next, Applicant's own conditions are so ill-defined that the Examiner would have to perform the experiment to determine those conditions that would provide for such stability at 40 deg C, however, from the claim, it would appear the structure is met, so the claim is still obvious, and its properties are inherent. Still further, the motivation to combine is found for other reasons, and hence, there is still the specific motivation found in the present obviousness type rejection to be addressed. Lastly, Applicant's "surprising" result is even drawn to abnormal conditions. 40 deg C is simply not a standard condition in which these compositions are stored. Lastly, what would be unusual is if these compositions did not have different stabilities as the conditions were changed, not that, given the myriad of conditions that could be changed, one specific composition has some increased stability under certain conditions, however ill-defined.

Applicant argues that Arginine with a chelator provides for increased stability over using longer polymers of arginine, like 80 monomers, and is due to improved attachment of DNA to the particles, as explained in the reply previously presented (p. 14, paragraph 3).

Such is not persuasive. The motivation is provided for the combination of elements. There is nothing new in using a chelating agent during the precipitation, and there is nothing new to using polyArginines of the range taught by Balhorn. There is motivation to utilize these specific polyArginines. Applicant has simply found another property which provides another

advantage to an already-obvious composition. Moreover, it is not absolute that the compoisition will have this property (e.g., TABLE 2). Hence, it would appear that the amendment is not an inherent property of the composition, and further, is not unexpected, as it appears to be reliant on something other than the specifics of the claims, if it is unexpected at all.

Applicant argues Sanford in a piecemeal fashion (pp. 14-15, paragraph bridging).

Such is not persuasive. As noted in the rejection, it is based on obviousness. Moreover, specific motivation is had, and its "inherent" properties, as Applicant's claims the unexpected properties to be, are necessarily inherent. A specific motivation to combine elements is simply not overcome by noting a particular property of the composition. This is not a non-specific motivation to combine.

Applicant argues that the polymers of Balhorn are noted to dissociate at a much quicker rate than the half-life of the particles of Applicant, and hence, it would not be expected to be efficacious in making stable particles (p. 15, paragraph 2).

Such is not persuasive. Applicant is misleading the argument. Applicant's particles have the DNA/protein complex precipitated onto the particle, and it is the same as in Sanford. The precipitate in either case does not release the protein from the nucleic acid. Once solvated and released, it releases the protein from the nucleic acid. If Sanford's particles were so unstable, they could not be utilized. However, Sanford teaches the particles sitting for 10 minutes or longer, then being washed and utilized. If the Spermidine was so unstable, it would not be possible to use it in the method, yet Applicant's own other arguments are just that: that spermidine is not as stable as that of polyarginine. However, This is simply not right. In this case, the particle precipitated compositions do not release with the kinetics of Balhorn, until it is

solvated into solution. With regard to arguments that the comments of Balhorn and EDTA being misplaced, the Examiner notes that this is a 103 rejection, and Sanford teaches EDTA. Lastly, going back to the argument that the increased dissociation rate would not be expected to work in the particles, it seems that Applicant's own specification seemed to choose arginines with an intent to have faster release, in a manner that suggests that Applicant understood the difference of release in solution, versus in the precipitate (e.g., Example 4, p. 34, penultimate paragraph).

Applicant argues that Oard is not in this rejection, however, is cited in rejections compounding on Sanford/Balhorn. Oard is alleged as used for teaching the use of gold to reduce clumping, but that Oard, like Sanford, utilizes spermine, and only suggests that polyLysine reduces clumping, however, such is only within the context of spermidine/CaCl2 precipitations, and Oard does not address the stability issues, because the compositions were used as soon as possible (pp. 15-16, paragraph bridging).

Such is not persuasive. The Art is taken in context of the skill of the Artisan. To argue that the Artisan was completely unable to utilize another known condensing agent seems to be beyond the Examiner's understanding. With regard to the properties found, such are inherent, and because the motivation is already specific for this combination, simply finding another property is only further characterization of an art-recognized obvious composition.

Applicant argues no reasonable expectation of success, arguing that Balhorns toroids are so completely different in structure, that the Artisan would not include it, because it decondenses more readily (p. 16, paragraph 2).

Such is not persuasive. As has been argued, the precipitate is not in solution, and hence, the decondensing takes place after it has been solvated from the surface of the microcarrier, much like Applicant's own tests of spermine and polyArg.

Applicant argues that the stability is a not expected, as the Artisan would have expected a decrease in stability due to the greater dissociation rate of Arginine polymers from the DNA (pp. 16-17).

Such is not persuasive. As has been discussed, the dissociation in solution is irrelevant, when precipitated onto the particle. Applicant is arguing that a distinct phase (solvated) of nucleic acid undergoes faster solvation, to argue that the precipitated phase is not stable. However, the stability of the precipitate does not revolve on the dissociation of the polyArg, or spermine, because it is precipitated. To wit, in the precipitated phase, the Arginine concentration is necessarily much higher, due to the exclusion of water, and hence, the off rate in solution is no longer applicable, because by increased chemical mass-action, the Arginine would immediately rebind.

Applicant argues that the Arts of Balhorn and Sanford are so distinct that one would have no reasonable expectation of success of combining the Arts, due to distinct methods of delivery (p. 16, paragraph 2).

Such is not persuasive. Balhorn and Sanford are both recognized to provide condensing of the DNA through the binding of a poly-cationic protein, as is well known in the Art. Sanford teaches the precipitation of the protein-nucleic acid complex onto a microcarrier, and Balhorn teaches that when in solution, the polyArg releases much faster than spermine. Why the Artisan

would not be able to combine these references, without a reasonable expectation of success, is beyond the Examiner's understanding.

Applicant argues that the Examiner has not supported his reasoning that the dissociation rate of Balhorn does not matter to the stability of the microcarrier particle (p. 16, paragraph 3).

Such is not persuasive. This is sort of a water-is -wet reference which is needed, but the Examiner will attempt to explain the simple logic, supplying art, and providing more reasoning. First, even as Applicant's claims and disclosure discuss, the nucleic acid/polyArg complex are placed onto the surface of the particle, in the presence of EDTA. The Artisan recognizes that in these particles, the protein/DNA is actually precipitated onto the surface. Such is evidenced even in Applicant's use of ethanol and/or calcium chloride. Applicant's own specification implies such an understanding of the process (Summary of the invention, paragraph 2; Example 4). Hence, it is taken for understood that the Art recognized that the protein/DNA complex was precipitated onto the surface of the particles. In Chemistry, a precipiate is a complex which forms by exclusion of solvent, thereby yielding a salt solid (i.e., removed solution) (e.g., http://www.chemicool.com/definition/precipitate.html#). When a composition is within a phase, such is the immediate environment. Given that water or solvent is largely excluded in this phase to allow for precipitation, the concentration of nucleic acid, and the concentration of protein, is greatly increased. For Example, water is typically at about 55 Molar in solution. Hence, exclusion of much of this water greatly increases the relative concentrations of nucleic acid and protein. Because of this, the dissociation of protein from nucleic acid is now governed by the equation [protein] + [nucleic acid] $\leftrightarrow$ [protein-nucleic acid]. Hence, by Mass Action, the equation now greatly favors the associated complex, rather than the protein and nucleic acid both

being in solution. In solution, however, the equation would be [water] + [protein-water] + [nucleic acid-water] ↔ [water] +[protein-nucleic acid-water]. Because, in this case, water concentration is so high, being approximately 55 molar, Mass Action will force the equation more toward the dissociated forms, versus the precipitate, as then the energy is minimized, due to mainly entropy. It is noted that the solvent need not be water, but is here, as it is most commonly the form which works for these precipitations. Therefore, the Examiner's statements have been correct.

Applicant argues that Examiner has not provided logic as to why polyArginine would be expected to condense DNA onto metal particles at all (p. 16, penultimate paragraph).

Such is not persuasive. The complex is made, as is shown in even Balhorn. With regard to precipitation, the use of CaCl2 or Ethanol are well known to be able to so-precipitate polycationic/DNA complexes (e.g., as shown in the rejection, referring to Sanford).

Applicant non-specifically cites Adami, et al. (1998) J. Pharm. Sci., 87: 678-83, to argue that it was surprising that shorter polymers of arginine woudl provide for increased stability (pp. 16-17, paragraph bridging).

Such is not persuasive. Adami's stability is drawn to solution forms of peptide/DNA condensates, not condensates which are precipitated onto a microparticle.

Applicant argues that Adami discusses lysines, which are argued to be acting the same way as arginines, as they both have high levels of positive charges on the polymer (p. 17, paragraph 2).

Such is not persuasive. Again, stability in solution to enzymes is distinct from the precipitate on a metal particle. Moreover, if Applicant's argument directly conflicts with the idea that the Artisan could not condense the DNA with polyarginine and precipitate it on the particle.

Applicant argues that protection from degradation is not a motivation to obviate the claims, but protection from degradation is the entire point of increased stability, And that therefore, because of Adami, longer polymers would be called for, rather than the short polymers of Applicant's claims (p. 17, penultimate paragraph).

Such is not persuasive. In either case, the precipitate is relatively precluded from the action of proteases and stuff in serum. With regard to stability in solution, Applicant has not claimed the condensate in solution, but precipitated onto the metal carrier. Please do not confuse the condensate (protein-nucleic acid complexes) with that of the precipitate (a precipitate of complexes of protein-nucleic acid on the surface of a particle).

Applicant argues that the results demonstrate more than routine optimization, and in fact, when tested again and again, consistently provide for increased stability (pp. 17-18, paragraph bridging).

Such is not persuasive. It has been shown that there are embodiments tested which do not provide for the results obtained. Moreover, it has been shown the Artisan knew to utilize the various substances. Further, it has been shown that there is specific reasoning to demonstrate obviousness. Lastly, Applicant argues that the results demosntrate non-routine results, rather than optimization, but Applicant's own specification calls their results "optimization" (e.g., Example 4).

Applicant claims the time of storage is not required to be part of the claims (p. 18, paragraph 2).

Such is not persuasive. To argue that the particles which are specifically obvious for other reasons are non-obvious because of a newly-described property of those particles, is unfair to the Artisan (and therefore the public), as the Artisan is already understanding that he/she can utilize these particles.

Claim Rejections - 35 USC § 103, Sanford, Balhorn (Oard), Cherng

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 12-15, 17-30, 32, 37-40, 42-46, 67, 73, 79, 80, 82, and 83 remain rejected, and Claims 84 newly rejected, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, as applied to claims 1-5, 7, 12-13, 17-20, 22-30, 32-38, 42-45, 67, 73, and 84 above, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23 and Kwok, et al. (2000) International Journal of Pharmaceutics, 203: 81-88, as necessitated by amendment, and to strengthen the rejection.

With regard to Claims 1-5, 7, 12-13, 17-20, 22-30, 32-38, 42-45, and 67, as is shown above, Sanford and Balhorn, as further evidenced by Oard, make obvious the various aspects of the claims.

However, Sanford and Balhorn, as further evidenced by Oard, do not make obvious the use of gold particles, further condensed in the presence of sucrose.

On the other hand, Oard teaches the use of gold particles can reduce particle clumping (e.g., p. 249, paragraph bridging columns). Further, Cherng teaches that condensation of nucleic acids with cationic polymers is further stabilized for storage by the presence of sucrose during the condensation (e.g., ABSTRACT).

With regard to Claims 79, 82, and 83, as shown in the above rejection, from Balhorn, it is routine experimentation to arrive at tetraarginine peptides, as well as heptaarginine peptides.

With regard to Claim 80, as shown above, it was known to conduct the precipitations on the microparticle in the presence of EDTA.

Kwok teaches that, e.g., sucrose can be used in as an excipient to stablize DNA condensates (e.g., p. 82).

Hence, at the time of invention, it would have been obvious to modify the techniques of Sanford and Balhorn, as further evidenced by Oard, to use the gold particles of Oard to reduce clumping, and further to condense the DNA in the presence of sucrose as taught by Cherng/Kwok, to increase the stability of the condensed DNA over time. Moreover, the Artisan would have had a reasonable expectation of success, as Oard teaches that gold particles will reduce clumping and Cherng/Kwok taught that the sucrose present in the condensed solution would provide more stability.

Response to Argument – Sanford, Balhorn (Oard), Cherng/Kwok

Applicant's argument of 8/7/09 has been fully considered but is not found persuasive.

Applicant broadly refers to the arguments of the base rejection (pp. 18-19, paragraph bridging), and the same answers are made.

Applicant argues that Cherng utilzies another type of polymer (methacrylate-based polymers) which is "chemically dissimilar" to arginine polymers, and Cherg states "... these findings are stric[t]ly speaking only applicable for PDMAEMA-pCMV lacZ plasmid formulations...", and hence, Cherng cannot be applied to the other references cited (p. 19, paragraph 2).

Such is not persuasive. It is clear that Cherng was stating that the results themselves are only applicable to the system tested, as is clear, but he also states that the results "might be extended to other polyplex and lipoplex formulations", meaning that similar, but distinct results may be obtained with other polymers. Moreover, it is already well known in the Art to utilize sucrose or other excipients for stabilizing protein/DNA complexes (e.g., Kwok, et al. (2000) International Journal of Pharmaceutics, 203: 81-88, e.g., ABSTRACT, and p. 82, second paragraph). Sucrose and other sugars, particularly trehalose are well known excipients, for stabilizing biological substances. The use thereof here is nothing new.

Applicant argues that Cherng does not overcome the deficiencies of the base references (p. 9, penultimate paragraph)

Such is not persuasive. There is no deficiency to overcome.

Claim Rejections - 35 USC § 103, Sanford, Balhorn (Oard), Cherng, Barman(Livesey)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12-32, 37-46, 67-73, 76, 79, 80, 82, 83 and 84 remain and/or are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23, and Kwok, et al. (2000) International Journal of Pharmaceutics, 203: 81-88 as applied to claims 1-5, 7, 12-15, 17-30, 32-40, 42-46, 67, 73, 79, 80, 82, 83, and 84 above, and further in view of U.S. Patent Publication No. 2004/0142475 to Barman, et al, as further evidenced by U.S. Patent No. 6,194,136 to Livesey, et al., for reasons of record and to emphasize the arguments.

As shown above, Claims 1-5, 7, 12-15, 17-30, 32-40, 42-46, 67, 73, 79, 80, 82,83, and 84 are obvious over the Art cited, except the cited Art does not specifically teach the use of transgenes encoding therapeutic proteins, or the use of a combination of raffinose and sucrose to stabilize the DNA. Nor does the cited art teach or make obvious the transgenes encoding HPV, HIV, HSV2, HSV1 or Hepatitis B antigens.

On the other hand, Barman teaches that stabilizers such as saccharides may be used in combination to stabilize the nucleic acid protein complexes (e.g., paragraph 0054). Further,

Barman teaches that HPV, HIV, HBV, and HSV (which includes HSV1 and HSV 2), antigens can be the transgenes for expression of antigens (paragraph 0036). Still further, Barman teaches influenza virus antigens to induce antibody responses (e.g., paragraph 0117). Still further Livesey also demonstrates the general understanding in the Art that various stabilizers which are sugars include raffinose (DESCRIPTION OF THE PREFERRED EMBODIMENTS, paragraph 29).

Hence, at the time of invention, it would have been obvious to modify the cited Art with Barman to use both raffinose and sucrose in stabilizing the particles and/or to use the various cited virus proteins. The Artisan would have been motivated to do so as the art already recognized that the sugars could be used in combination and/or the various proteins could be expressed for making antigens. Moreover, the Artisan would have had a reasonable expectation of success, as the Art already recognized the efficacious effect of saccharides.

Response to Argument – Sanford, Balhorn (Oard), Cherng/Kwok, Barman(Livesey)

Applicant's argument of 8/7/09 has been fully considered but is not found persuasive.

Applicant argues that Barman fails to overcome the deficiencies of the base references (p. 20, penultimate paragraph).

Such is not persuasive. There are no such deficiencies.

Claim Rejections - 35 USC § 103 – many references

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12-32, 37-46, and 67-83 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23, and Kwok, et al. (2000) International Journal of Pharmaceutics, 203: 81-88 and U.S. Patent Publication No. 2004/0142475 to Barman, et al, as further evidenced by U.S. Patent No. 6,194,136 to Livesey, et al., as applied to claims 1-7, 12-32, 37-46, 67-73, 76, 79, 80, 82, and 83 above, and further in view of the knowledge of the Artisan as evidenced by (i) Ramos, et al. (1997) Applied and Environmental Microbiology (e.g., ABSTRACT); (ii) Ericksson, et al. (2003) Pharmaceutical Research, 20(9): 1437-43 (e.g., ABSTRACT); (iii) Kaushik, et al. (2003) Journal of Biological Chemistry, 278(29): 26485-65 (e.g., ABSTRACT); (iv) Garg, et al. (2002) Proceedings of the National Academy of Science, USA., 99(25): 15898-903 (e.g., ABSTRACT); (v) More, et al. (1998) Hindustan Antibiotics Bulletin, 40(1-4): 1-4 (ABSTRACT ONLY); (vi) Joshi, et al. (2001) AAPS PharmSciTech., 2(4): 25 (ABSTRACT ONLY), Ruan, et al. (2003) European Journal of Biochemistry, 270: 1654-61 (e.g., ABSTRACT), and Schellman (2003) Biophysical Journal, 85(1): 108-25.

As shown above, the various references obviate the various claims, however, Claims 74, 75, 77, and 78 introduce the requirement of trehalose as the sugar, and the combination of gold particles precipitated with DNA in the presence of polyarginine, EDTA, and trehalose. Hence, the new aspect is essentially the use of trehalose.

However, as shown by the abstracts of (i) Ramos, et al. (1997) Applied and Environmental Microbiology, 63(10): 4020-25 (e.g., ABSTRACT); (ii) Ericksson, et al. (2003) Pharmaceutical Research, 20(9): 1437-43 (e.g., ABSTRACT); (iii) Kaushik, et al. (2003) Journal of Biological Chemistry, 278(29): 26485-65 (e.g., ABSTRACT); (iv) Garg, et al. (2002) Proceedings of the National Academy of Science, USA., 99(25): 15898-903 (e.g., ABSTRACT); (v) More, et al. (1998) Hindustan Antibiotics Bulletin, 40(1-4): 1-4 (ABSTRACT ONLY); (vi) Joshi, et al. (2001) AAPS PharmSciTech., 2(4): 25 (ABSTRACT ONLY), and (vi) Ruan, et al. (2003) European Journal of Biochemistry, 270: 1654-61, many sugars, and especially Trehalose is known to stabilize proteins, especially when the product is being dried. Still further, this stabilizing force is even generally understood to be due to the changes in excluded volume and contact interaction with the surface protein, which is increased in the presence of sugars in general, and shown in Schellman (2003) Biophysical Journal, 85(1): 108-25, (e.g., ABSTRACT). Given this, it is clear that the Artisan would have understood that the molecules would be stabilized in the presence of various sugars, and particularly trehalose and sucrose.

Hence, it would be obvious to perform the various steps with trehalose, or really any particular sugar. The Artisan would do because it would allow increased stability to be imparted to the dried particles, and thereby allow their half-life to be increased. Moreover, the Artisan would have a reasonable expectation of success, as the Artisan knew that trehalose was efficient at stabilizing such.

Response to Argument – Sanford, Balhorn (Oard), Cherng/Kwok, Barman(Livesey) and Various Other References

Applicant's argument of 8/7/09 has been fully considered but is not found persuasive.

Applicant argues that the Artisan would not have been motivated to use the arginine rich fast-dissociation peptides of Balhorn in the ballistic delivery methods of Sanford or Oard (p. 21, paragraph 2).

Such is not persuasive. Broad argument does not supplant the need to provide specific reasoning and/or data to make the argument valid.

Applicant argues that the various references are not directed to any particular technology like the particles, and thus is not relevant (p. 21, penultimate paragraph).

Such is not persuasive. The purpose for the multi-faceted technological application to demonstrate that the sugars are stabilizers, and further emphasized by Schellman, demonstrating that the Artisan understood its wide-applicability, demonstrates that it is reasonably predicted to work with the particles: it always works.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Primary Examiner, Art Unit 1633